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Histological Changes of Spleen and Liver in Experimental Portal Hypertension Produced by Anti-Dog-Spleen Rabbit Serum

by

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CONTENT

I. INTRODUCTION

A disease beginning with anemia and splenomegaly and terminating with atrophic cirrhosis of the liver was first distinguished from other resembling diseases in 1894 by BANTI[3)4)], which was thereafter called Banti's disease and became to be considered as an independent disease unit. As the studies on this disease were accumulated, independency of this disease as a disease unit became to be suspected and there arose many discussions particularly on its identity with LAENNEC's cirrhosis[26)35)]. Provided that the original definition of this disease made by BANTI might be corrected to some extent, it is of utmost interest from clinical and pathological aspects to consider the problem whether this disease should be comprehended as a syndrome or as a disease unit. If one succeeds in seeking the etiologic factor of this disease in the spleen, it might be said that independency of this

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disease exactly approving of the original assertion of BANTI is demonstrated. However, there is none that fulfils these conditions both clinically and experimentally.

Researchers of the Presbyterian Hospital[40)52)], as ROUSSELOT, WHIPPLE and THOMPSON, classified portal hypertension from etiologic aspect into portal hypertension with intrahepatic cause and one with extrahepatic cause, and as the representative of the former they pointed out liver cirrhosis and as the representative of the latter so-called Banti's disease. Moreover, they came to insist that extrahepatic obstruction of the portal vein was the real cause of this disease[56)], and many experimental and clinical observations were done from this point of view. It is, however, well known that the results of all these observations were rather disappointing.

On the other hand in our country, SUZUKI[48)58)] succeeded in producing a pathological conditions resembling so-called Banti's disease by protracted sensitization of rabbits with egg white albumin. In his experiment, there remains the problem how the allergic stimulations given to the entire body are confined to the spleen and liver, and some differences of the disease picture from clinical one are pointed out such as occurrence of considerably intense pathological changes in the kidney and elsewhere and the fact that provocative factor is required for elevation of portal pressure.

In the aim of selectively impairing splenic tissue, anti-dog-spleen rabbit serum (abbreviated to anti-spleen serum, hereafter) produced by immunizing rabbits with homogenate of dog spleen was repeatedly injected intravenously in dogs, and observations were done in these dogs. At the same time, some consideration were done on the relation of the findings of the present experiment and so-called Banti's disease.

II. MATERIALS AND METHODS (Fig. 1)

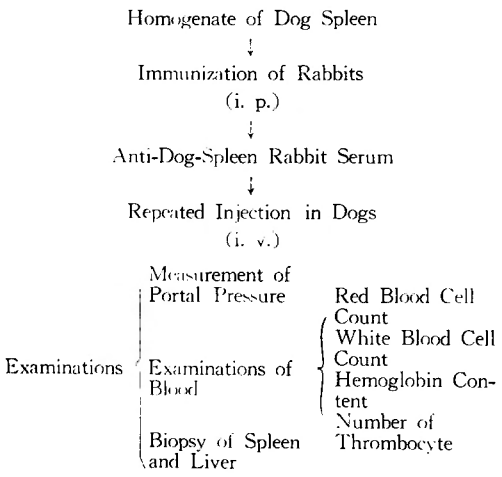


Fig. 1 Summary of Experimental Procedures

1. Experimental Animals

Adult mongrel dogs, weighing from 8 to 13 kg, of both sexes were used. For the production of anti-spleen serum, adult rabbits of both sexes weighing from 2.5 to 4 kg were used.

2. Preparation of Antigen for Immunization of Rabbits

In dogs weighing from 8 to 10 kg, 1,000 biological units of heparin was previously injected intravenously[41)]. The abdomen was opened with upper median incision under intravenous anesthesia of Isozol of 15 to 20 mg/kg body weight. The spleen was extirpated under aseptic conditions. The splenic pedicle was preseved as long as possible on the splenic side for the convenience of perfusion carried out later, and the small vessels other than the splenic artery and vein were deliberately ligated. The following procedures of the perfusion were invariably carried out under aseptic conditions. Polyethylene tubes were inserted into the splenic artery and vein, respectively,

and the spleen was perfused with saline solution of 8 to 10 l under the pressure of 100 cc syringe. As the blood within the spleen was washed out by perfusion the spleen became pale and transparent. Then, the capsule and soft tissue of the splenic hilum were removed and the parenchyma was well ground by Waring's blender and glass homogenizer and made into 20 per cent homogenate being diluted with saline solution. The homogenate was stored at 4 C, with Marzonine added to be 0.01 per cent in final concentration. This was used as the antigen for immunization of rabbits.

3. Immunization of Rabbits and Withdrawal of Blood

Homogenate of dog spleen of 2 cc, prepared as described in the above, was intraperitoneally injected in rabbits every 3 days. The injection for immunization was repeated from 9 to 12 times[31]. Seven days after the accomplishment of the immunization, the rabbit was anesthetized with ether and the thoracic cavity was opened. Blood was withdrawn by heart puncture and the blood was placed quietly for 24 hours at 4°C for separation of serum.

4. Absorption and Removal of Non-Organ Specific Antibodies in Anti-Spleen Serum

Serum of immunized rabbit was incubated at 56°C for 30 minutes to inactivate complement, then blood corpuscles of dog, taken with anticoagulant and rinsed with saline adequately, and well minced muscle of dog, also well rinsed with saline, were added and incubated at 37°C for 60 minutes for absorption and removal of non-organ specific antibodies. The mixture of serum, blood corpuscles and muscle was centrifuged at 3,000 r.p.m. for 30 minutes. Anti-spleen serum was obtained as the supernatant of the above mentioned centrifugation, which was stored at 4°C with a preservative of Marzonine in 0.01 per cent.

For the control study, normal rabbit serum was used instead of anti-spleen serum. Normal rabbit serum for the control study was similarly subjected to inactivation of complement and absorption of non-organ specific antibodies, Marzonine being added in 0.01 per cent, and it was stored at 4°C.

5. Serological Certification of Anti-Spleen Serum

Determination of antibody titer of anti-spleen serum was performed in each of individual serum, by overlying precipitation method against corresponding antigen of dog spleen homogenate. Anti-spleen serum was diluted with 2 per cent gum-arabic saline solution for precipitation test. Since the antigen solution of dog spleen homogenate contained so much cellular components which disturb the reading of precipitation, it was centrifuged at 3,000 r.p.m. for 30 minutes prior to the test and the supernatant was filtered with Seitz filter by suction, using filter paper of No.85 of Toyo Roshi Co. Ltd.

The similar procedures were carried out on antigen of dog liver homogenate for detection of cross reaction antibody between anti-spleen serum and the liver of dog.

6. Injection of Anti-Spleen Serum

Anti-spleen serum of 1 cc/kg body weight was injected every 7 days intravenously in the upper or lower extremity of dog.

Anti-spleen serum was stored not as individual serum but as pooled serum, and prior to the injection it was centrifuged at 3,000 r.p.m. for 10 minutes to remove minute particles contained in it.

7. Examinations of Peripheral Blood

Before and after the injection of anti-spleen serum, hemoglobin content, red blood cell count, white blood cell count and thrombocyte count were determined every 50 to 100 days. Red and white blood cell count were performed using a hemocytometer of THOMA, and hemoglobin content was determined following the method of SAHLI. The methods of FONIO and KATASE were employed for determination of thrombocyte count, and for the accuracy of the determination, thrombocytes were counted in the microscopic field covering 5,000 of red blood cells.

8. Measurement of Portal Pressure

At least 10 days before the commencement of anti-spleen serum injection, the abdomen of dog was opened with upper median incision under anesthesia of intravenous injection of Isozol of 15 mg/kg body weight. A polyethylene tube of 1 mm in caliber was inserted from a branch of the superior mesenteric vein to the portal vein, which was connected to an aqueous manometer filled with saline solution containing heparin of 1,000 biological units per 500 cc of saline. Zero point of the manometer was adjusted to be in the level of the entrance of the portal vein to the liver. Measurement of portal pressure was repeated 3 times under as similar condition as possible, and the average value was taken[57].

After the commencement of the injection of anti-spleen serum, portal pressure was measured in the same way every 3 to 4 months. For postoperative observations, the injection of anti-spleen serum was interrupted for 20 days after laparotomy for measurement of portal pressure.

9. Biopsy of the Spleen and Liver and Histological Studies

At the above mentioned laparotomy for measurement of portalpressure, small pieces of the spleen and liver were taken in a shape of wedge from the marginal part of these organs, and the cut surface was ligated with silk-threads previously inserted in this area, by which procedures artificial congestion within the pieces of the tissue was prevented. Pieces of the tissue were immediately fixed in a 10 per cent formalin solution and embedded in paraffin. Microscopic sections of the spleen were made 3 to 5 μ in thickness, and those of the liver 6 to 8 μ in thickness. Both of these were stained with hematoxylin and eosin or with silver impregnating method of GOMORI for histological studies.

III. RESULTS

1. Serological Certification of Anti-Spleen Serum (Tab. 1)

Antibody titer of anti-spleen serum against corresponding antigen of spleen was determined by overlying precipitation method every time of production of the serum. Antibody titer ranged from 2^6 to 2^8, and antigen dilution of these test tubes were 80 to 320 times. At the same time, it was ascertained that positive reaction of the precipitation disappears when the antibody was absorbed by splenic tissue of dog. Antibody titer of anti-spleen serum against antigen of dog liver was approximately 2^4, which also disappeared, however, by the absorption with splenic tissue.

2. Changes in Peripheral Blood

i) Red Blood Cell (Tab. 2, Fig. 2)

Tab. 1 Precipitation Test

Anti-Spleen Serum	Antigen (Dog Spleen Homogenate) 40	80	160	320	640	1280	C
2	++	++	+	+	±	−	−
4	++	++	+	+	−	−	−
8	++	++	+	+	−	−	−
16	++	+	+	±	−	−	−
32	+	+	+	±	−	−	−
64	+	+	±	−	−	−	−
128	+	+	±	−	−	−	−
256	−	−	−	−	−	−	−
512	−	−	−	−	−	−	−
C	−	−	−	−	−	−	−

Red blood cell count was 620×10^4 to 695×10^4, 659×10^4 on the average, before the injection of anti-spleen serum. It was 530×10^4 to 640×10^4, 579×10^4 on the average, 50 days after the commencement of the injection. It was 535×10^4 to 670×10^4, 607×10^4 on the average, 150 days after the commencement of the injection. It was 490×10^4 to 675×10^4, 610×10^4 on the average, 250 days after the commencement of the injection. It was 625×10^4 to 643×10^4, 634×10^4 on the average, 350 days after the commencement of the injection. Namely, red blood cell count obviously decreased after the commencement of the injection of anti-spleen serum, showing its minimum value at 50th day, which, however, showed gradual increase thereafter, but it did not restore to the value before the injection as late as 350 days after the commencement of the injection.

In control animals receiveing injection of normal rabbit serum, red blood cell count was 580×10^4 to 675×10^4, 630×10^4 on the average, before the injection. Fifty days after the commencement of the injection, it was 600×10^4 to 685×10^4, 635×10^4 on the average. It was 585×10^4 to 735×10^4, 639×10^4 on the average, 150 days after the commencement of the injection. It was 565×10^4 to 731×10^4, 639×10^4 on the average, 250 days after the commencement of the injection. It was 610×10^4 to 710×10^4, 657×10^4 on the average, 350 days after the commencement of the injection. Thus, red blood cell count showed little change in the group of control animals.

ii) Hemoglobin Content (Tab. 3, Fig. 3)

Before the injection of anti-spleen serum, hemoglobin content was 86 to 95 per cent, 89 per cent on the average. It was 58 to 80 per cent, 69 per cent on the average, 50 days after the commencement of the injection. It was 58 to 97 per cent, 77 per cent on the average, 150 days after the commencement of the injection. It was 57 to 90 per cent, 73 per cent on the average, 250 days after the commencement of the injection. It was 70 to 77 per cent, 74 per cent on the average, 350 days after the commencement of the injection. Namely, hemoglobin content decreased with the commencement of the injection of anti-spleen serum and maintained the decreased level.

In control animals, hemoglobin content was 76 to 90 per cent, 81.2 per cent on the average, before the injection. It was 76 to 92 per cent, 81.6 per cent on the average,

Tab. 2 Red Blood Cell Count ($\times 10^4$)

	Dog No.	Before	Days After Injection				
			50	150	250	350	450
Experimental Group	61	687	530	535	640	643	515
	101	652	602	595	595	—	—
	103	695	640	670	675	625	—
	104	620	545	625	650	—	—
	111	642	560	612	490	—	—
	Mean	659	579	607	610	634	515
Control Group	21	604	625	646	640	634	—
	22	675	685	735	731	710	—
	23	580	600	585	565	—	—
	24	660	655	640	634	675	—
	25	632	609	590	625	610	—
	Mean	630	635	639	639	657	—

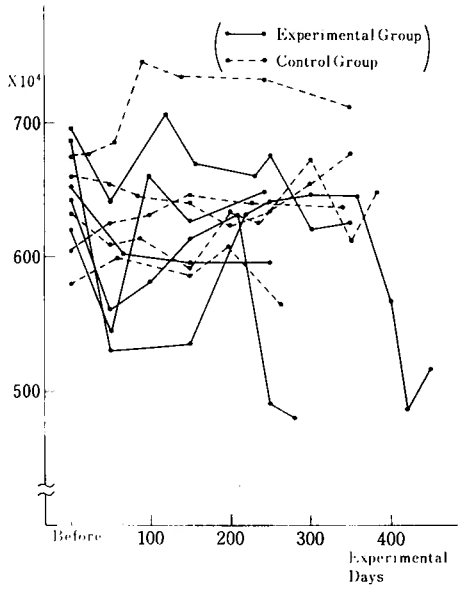


Fig. 2 Red Blood Cell Count

50 days after the commencement of the injection. It was 74 to 92 per cent, 82 per cent on the average, 150 days after the commencement of the injection. It was 69 to 88 per cent, 75.2 per cent on the average, 250 days after the commencement of the injection. It was 73 to 89 per cent, 82.5 per cent on the average, 350 days after the commencement of the injection. Changes could be hardly observed in hemoglobin content in the group of control animals.

iii) White Blood Cell (Tab. 4, Fig. 4)

White blood cell count was 11,200 to 16,000, 13,000 on the average, before the injection of anti-spleen serum. It was 11,000 to 18,200, 15,500 on the average, 50 days after the commencement of the injection. It was 11,200 to 19,000, 15,500 on the average, 150 days after the commencement of the injection. It was 10,500 to 38,700, 23,900 on the average, 250 days after the commencement of the injection. It was 13,600 to 24,300, 19,000 on the average, 350 days after the commencement of the injection. Particularly marked increase in white blood cell count was considered to be attributable to bacterial contamination at laparotomy, and excluding these cases, significant fluctuation in white blood cell count could not be observed.

In animals of the control, white blood cell count was 10,200 to 20,600, 15,580 on the average, before the injection of normal rabbit serum. It was 10,000 to 20,000, 16,560

Tab. 3 Hemoglobin Content (%)

	Dog No.	Before	Days After Injection				
			50	150	250	350	450
Experimental Group	61	95	58	58	57	77	64
	101	86	75	70	68	—	—
	103	87	64	97	85	70	—
	104	88	68	84	90	—	—
	111	94	80	78	64	—	—
	Mean	89	69	77	73	74	64
Control Group	21	90	92	92	88	89	—
	22	78	83	90	88	87	—
	23	76	76	79	75	—	—
	24	79	77	75	69	81	—
	25	83	80	74	76	73	—
	Mean	81	82	82	75	83	—

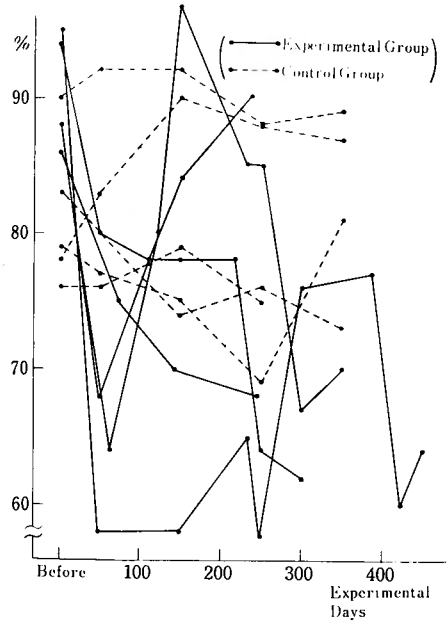


Fig. 3 Hemoglobin Content

on the average, 50 days after the commencement of the injection. It was 12,900 to 22,000, 17,580 on the average, 150 days after the commencement of the injection. It was 14,000 to 23,400, 18,140 on the average, 250 days after the commencement of the injection. It was 17,000 to 25,000, 19,900 on the average, 350 days after the commencement of the injection. White blood cell count in control group also showed little significant changes.

iv) Thrombocyte (Tab. 5, Fig. 5)

Thrombocyte count was 18.4×10^4 to 27.1×10^4, 22.0×10^4 on the average, before the injection of anti-spleen serum. It was 3.5×10^4 to 15.7×10^4, 9.1×10^4 on the average, 50 days after the commencement of the injection. It was 6.5×10^4 to 15.4×10^4, 11.1×10^4 on the average, 150 days after the commencement of the injection. It was 9.3×10^4 to 22.5×10^4, 12.9×10^4 on the average, 250 days after the commencement of the injection. It was 6.6×10^4 to 19.9×10^4, 13.2×10^4 on the average, 350 days after the commencement of the injection. Thrombocyte showed a rapid decrease after the commencement of the injection without tendency of restoration to the value before the injection.

In animals of control group, thrombocyte count was 19.2×10^4 to 25.3×10^4, 22.6×10^4 on the average, before the injection of normal rabbit serum. It was 18.2×10^4 to 24.9×10^4, 21.6×10^4 on the average, 50 days after the commencement of the injection.

Tab. 4 White Blood Cell Count

	Dog No.	Before	Days After Injection				
			50	150	250	350	450
Experimental Group	61	11800	11000	11200	30000	24300	17200
	101	14200	18200	19000	22000	—	—
	103	16000	17600	16600	38700	13600	—
	104	12000	17200	16200	18600	—	—
	111	11200	13700	14600	10500	—	—
	Mean	13000	15500	15500	23900	19000	17200
Control Group	21	16400	14000	18000	16000	17000	—
	22	12700	19400	12900	14300	17600	—
	23	10200	10000	14000	14000	—	—
	24	18000	20000	21000	23000	20000	—
	25	20600	19400	22000	23400	25000	—
	Mean	15580	16560	17580	18140	19900	—

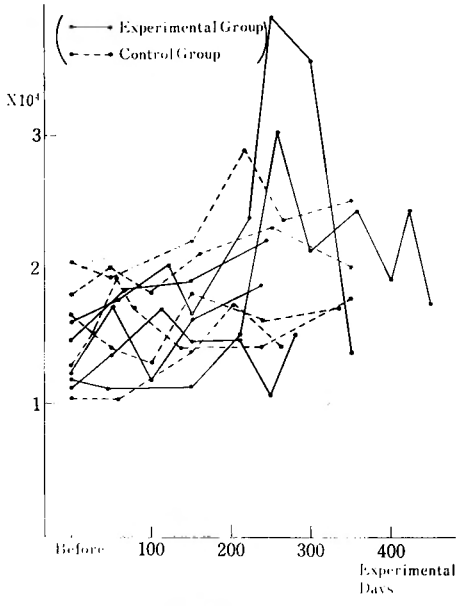


Fig. 4 White Blood Cell Count

It was 19.7×10^4 to 25.1×10^4, 22.3×10^4 on the average, 150 days after the commencement of the injection. It was 15.2×10^4 to 24.6×10^4,20.3×10^4 on the average, 250 days after the commencement of the injection. It was 18.8×10^4 to 24.6×10^4, 21.3×10^4 on the average, 350 days after the commencement of the injection. Little fluctuation could be observed in thrombocyte count in control group.

3. Changes in Portal Pressure (Tab. 6, Fig. 6)

As early as 3 days after the injection of anti-spleen serum, portal pressure increased, which showed further elevation following continuation of the injection.

In the dog No.61, for instance, portal pressure was 90mmH_2O before the injection of anti-spleen serum, which fluctuated to be 145 mmH_2O at 49 th day, 95 mmH_2O at 89th day, 200 mmH_2O at 185th day, 215 mmH_2O at 231st day, 205 mmH_2O at 269th day, 205 mmH_2O at 304th day and 195 mmH_2O at 450th day.

Here, portal pressure at 89th day was measured after an interruption of the injection for 40 days, and it is worth while mentioning that the portal pressure showed as low a level as initial one.

In the dog No.101, initial portal pressure was 110 mmH_2O, then it fluctuated to be 175 mmH_2O at 73rd day, 190 mmH_2O at 142nd day and 200 mmH_2O at 230th day.

Tab. 5 Number of Thrombocyte ($\times 10^4$)

	Dog No.	Before	Days After Injection				
			50	150	250	350	450
Experimental Group	61	23.0	6.0	6.5	9.7	19.9	11.3
	101	27.1	15.7	13.1	12.4	—	—
	103	21.0	12.2	15.4	10.4	6.6	—
	104	18.4	3.5	7.5	22.5	—	—
	111	20.6	8.5	11.2	9.3	—	—
	Mean	22.0	9.1	11.1	12.9	13.2	11.3
Control Group	21	21.0	24.5	22.5	19.5	18.8	—
	22	25.3	21.9	25.1	22.0	22.3	—
	23	22.0	20.0	21.5	15.2	—	—
	24	19.2	20.3	22.6	20.0	21.6	—
	25	22.5	18.2	19.7	21.6	19.4	—
	Mean	22.6	21.6	22.3	20.3	21.3	—

Fig. 5 Number of Thrombocyte

In the dog No.103, portal pressure was 120 mmH_2O before the injection, which was followed by fluctuation as to be 165 mmH_2O at 30th day, 180 mmH_2O at 71st day, 185 mmH_2O at 158th day, 180 mmH_2O at 259th day and 180 mmH_2O at 336th day. In the dog No.104, initial portal pressure was 120 mmH_2O and it fluctuated thereafter to be 185 mmH_2O at 24th day, 165 mmH_2O at 63rd day, 185 mmH_2O at 151st day and 190 mmH_2O at 215th day. In the dog No.111, initial portal pressure was 110 mmH_2O and it fluctuated to be 150 mmH_2O at 52nd day, 145 mmH_2O at 124th day and 155 mmH_2O at 220th day. In the dog No.12, initial portal pressure was 100 mmH_2O and it fluctuated to be 120 mmH_2O at 26th day and 150 mmH_2O at 56th day.

In control dog of No.21, initial portal pressure was 95 mmH_2O and it fluctuated to be 115 mmH_2O at 26th day, 110 mmH_2O at 150th day, 105 mmH_2O at 210th day and 110 mmH_2O at 310th day. In the control dog of No.22, initial portal pressure was 115 mmH_2O and it was followed by the fluctuation as to be 110 mmH_2O at 32nd day, 120 mmH_2O at 81st day, 125 mmH_2O at 125th day, 140 mmH_2O at 225th day and 140 mmH_2O at 305th day. In the control dog of No.23, initial portal pressure was 105 mmH_2O and it fluctuated to be 110 mmH_2O at 74th day, 115 mmH_2O at 150th day, 110 mmH_2O at 205th day and 125 mmH_2O at 324th day.

Tab. 6 Portal Pressure after Injection of Anti-Spleen (mmH_2O)

	Dog No.	Before	( ) : Days after Injection ~100	~200	~300	~400	More than 400 Days
Experimental Group	61	90	(49) 165	(185) 200	(231) 215 (269) 205	(304) 205	(450) 195
	101	110	(83) 175	(142) 190	(230) 200	—	—
	103	120	(30) 165 (71) 180	(158) 185	(259) 180	(336) 180	—
	104	120	(24) 185 (63) 165	(151) 185	(215) 190	—	—
	111	110	(52) 150	(124) 145	(220) 155	(320) 175	—
	121	100	(26) 120 (56) 150	(160) 165	(240) 170	(340) 185	—
Control Group	21	95	(26) 115	(150) 110	(210) 105	(310) 110	—
	22	115	(32) 110 (31) 120	(125) 125	(225) 140	(305) 140	—
	23	105	(74) 110	(150) 115	(205) 110	(324) 125	—
	24	120	(25) 130	(107) 135	(210) 125	(315) 130	—
	25	115	(30) 120	(130) 135	(220) 140	(330) 145	—

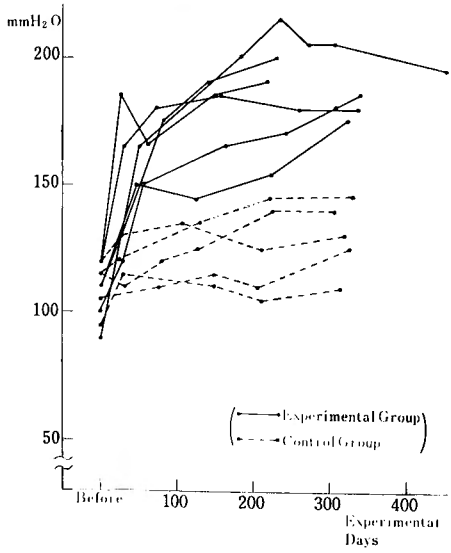


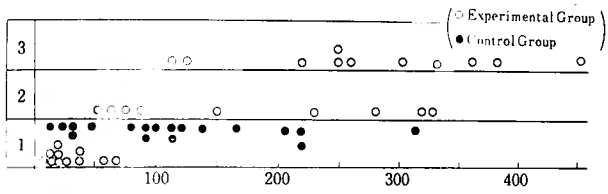
Fig. 6 Portal Pressure after Injection of Anti-Spleen Serum

4. Histological Findings of the Spleen and Liver

i) Spleen

Although there could not be observed splenomegaly in the course of the experiment, there appeared thickening of the splenic capsule as the experimental days were accumulated, and the spleen showed a tendency of shrinkage partly owing to the adhesion with the omentum.

Histological findings of the spleen are summarized as in (Fig. 7). Transition of histological changes in the spleen can be classified roughly in 3 patterns. The first pattern of the change was observed until 100th day of the experiment, and it was characterized by intense proliferation of large mononuclear cells, polymorphnuclear leucocytes and



1. Marked reactive increase in phagocytes, leucocytes and large mononuclear cells.
2. Marked reactive increase in plasma cells and reticulum cells.
3. Atrophic or fibrotic changes

Fig. 7 Summary of Histological Findings of the Spleen

phagocytes. The splenic follicles were large, and although proliferation of the above mentioned leucocytes was observed in the splenic red pulp, size of the splenic sinuses was normal, sinus endothelium showing tendency of swelling. In some cases, extreme atrophy or disappearance of follicles, intense infiltration of leucocytes in the red pulp with necrotic foci of various sizes and thickening of the capsule could be observed, which was accepted to be the picture of acute splenitis. The second pattern of the changes could be observed from 50th to 200th day of the experiment, being confined within this period. It is characterized by marked increase in plasma cells and reticulum cells, intense proliferation of follicles and remarkable increase in plasma cells in conglomeration in red pulp with scattered islet-like increase in reticulum cells. Wall of the follicular artery was somewhat edematous and sinus endothelium showed a tendency of proliferation, being swollen. The third pattern of the changes was characterized by atrophic change or fibrotic proliferative change, which was observed in animals survived more than 100 experimental days. The follicles were non-proliferative and almost disappeared. Marked finding was increase in spindle-shaped cells in red pulp. Endothelium of the sinus and vessel was swollen and showed the tendency of proliferation. Some of the splenic sinuses showed the tendency of narrowing. By the silver impregnating method, large lattice fibre could be observed around the trabecle, vessel wall and sinus, extending to the surroundings. These pattern of the changes developed from the first to the second, and from the second to the third.

In animals of control group, the first pattern of the changes in experimental animals could be at most observed, revealing proliferation of wandering cells of various kind. Of course, neither the picture of acute splenitis nor fibrous proliferation could be observed in control group.

ii) Liver

Pathologic change of the liver appeared towards 100th experimental day. Infiltration of polymorphnuclear leucocytes and lymphcytes could be observed around the Glisson's sheaths, which was gradually modified by intermingling of phagocytes and plasma cells. Although Kupffer cells were observed to be swollen, any pathologic change could not be observed in liver cells. Narrowing or obstructive deformity of the intrahepatic vessels could not be observed. What was characteristic in the liver findings was that even in the stadium of marked changes in the spleen, significant changes were hardly observed in the liver. In the finding of silver impregnation, changes of the fibrous component could not be observed

generally, but in cases of marked cellular infiltration thickening of lattice fibre, particularly that of the interlobular connective tissue could be observed in some part, suggesting collagenization.

Changes of the liver in control group were more slight compared with that in experimental animals, at most showing infiltration of polymorphnuclear leucocytes and lymphoid cells around the vessels

Besides these, the kidney of the lethal cases was histologically studied, but significant pathologic change could not be found.

5. Relationship between Portal Pressure and Number of Thrombocytes (Fig. 8)

As described in the above, portal pressure increased as early as 3 days after the injection of anti-spleen serum. Thrombocytes already decreased markedly in this period in peripheral blood. There could be observed close correlation between portal pressure and thrombocyte number, i. e. portal pressure was 90 to 120 mmH_2O before the injection of anti-spleen serum and thrombocyte number was 19×10^4 to 26×10^4 at this stadium, and at the stadium of portal hypertension of 180 mmH_2O to 210 mmH_2O, thrombocyte number was 8×10^4 to 12×10^4.

6. Relationship between Portal Pressure and Histological Findings of the Spleen and Liver

As described in the above, elevation of portal pressure could be observed following the repeated injection of anti-spleen serum, the degree of which was 215 mmH_2O in the maximum and there could not be observed any more increase in portal pressure, even if

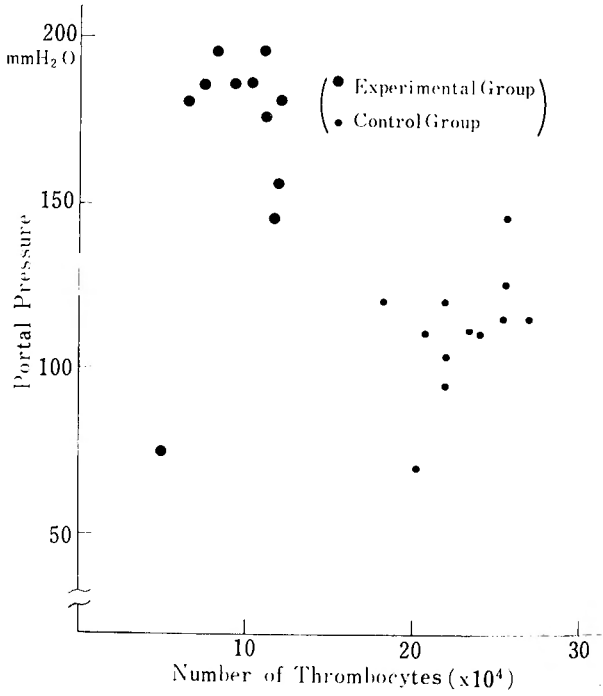


Fig. 8 Portal Pressure and Thrombocyte

the injection of anti-spleen serum was more accumulated. However, in the histological findings, a series of pathologic change developed in the spleen from proliferation of wandering cells to atrophic and fibrotic changes through proliferation of plasma cells and reticulum cells. On the other hand, significant changes could not be observed in the initial stadium in the liver, and moreover, changes observed thereafter was far more slight than in the spleen, at most revealing infiltration of various cells.

In the following, some cases revealing typical histological changes are presented.

Case 1: In the dog No. 57, initial portal pressure was 108 mmH_2O, and it increased to 180 mmH_2O 3 days after 2 injections of anti-spleen serum. In the spleen of this stadium intense congestion was observed in general, follicles being extremely atorphic, hemosiderin, phagocytes and polymorphnuclear leucocytes being increase in the red pulp in moderate degree, and plasma cells could not be found and proliferation of reticulum cells was in the slightest degree with thickening of the capsule, revealing the picture of splenitis. In the liver of the same stadium, degree of changes was mild merely revealing small conglomerations of large mononuclear cells and polymorphnuclear leucocytes in the lobules. (Fig. 9 and 15)

Case 2: In the dog No. 61, initial portal pressure was 90 mmH_2O and it increased to 215 mmH_2O 3 days after 25 injections of anti-spleen serum. Thickening of the capsule could be observed in the spleen, and increase in cellular components was observed in the red and white pulp, most of which was consisted of plasma cells and or reticulum cells. Particularly, plasma cells formed small conglomerations in some areas. Swelling of the vascular and sinus endothelium could be also observed. Although there were some areas seemingly accepted to be fibrosis, marked changes could not be recognized by silver impregnation. In the liver, significant changes could not be found, at most revealing slight swelling of the Kupffer cells here and there. (Fig. 10)

Case 3: In the dog No. 101, initial portal pressure was 110 mmH_2O, and it increased to 175 mmH_2O 3 days after 12 injections of anti-spleen serum. The size of the splenic follicles was normal. Although proliferation of reticulum cells could be observed in the red pulp, infiltration of plasma cells and polymorphnuclear leucocytes could not be observed. In the white pulp or splenic sinus, hemosiderin granules were observed here and there. Vascular endothelium showed swelling in some part and the vessels were edematous. In the silver impregnation findings, the lattice fibres increased their size in the red pulp and the number of these fibres also increased. Such changes were particularly remarkable around the trabecle, sinus and vessels. However, normal net-work structure of the spleen was preserved. In the liver, infiltration of neutrophils, lymphocytes and phagecytes was observed around the vessels in the Glisson's sheaths, but infiltration of plasma cells was in a slight degree, the vessels of the Glisson's sheath themselves showing no significant change. Narrowing or obstructive deformity of the central vein, of course, could not be observed. In the silver impregnating findings, the lattice fibres increased their size in general, and in some area, thickening of the interlobular connective tissue could be observed with a tendency of collagenization. (Fig. 11, 13, 14 and 16)

Case 4: In the dog No. 111, initial portal pressure was 110 mmH_2O, and it elevated to 155 mmH_2O 3 days after 23 injections of anti-spleen serum. In the spleen, size of the

follicles in the white pulp was normal, and the splenic pulp was generally atrophic, without cellular infiltration or cellular proliferation. At most, small masses of plasma cells could be observed around the follicles and vessels, and phagocytes were also few. By the silver impregnating study, slight increase in the lattice fibre was observed around the follicles and vessels. In the liver, althogh infiltrative increase in plasma cells and leucocytes could be observed around the vessels, swelling of Kupffer cells could hardly be observed. Silver impregnating study of the liver revealed slight increase in the lattice fibre in the interspace of the lobules. (Fig. 12, 17, 18, 19 and 20)

IV. DISCUSSION

In 1866, GRESTEL observed a case of anemia accompanied by splenomegaly and described this as *anemia splenica*[14]. In 1883, BANTI[3] pointed out the existence of anemia accompanied by splenomegaly from unknown cause and he insisted that this lesion can be obviously distinguished from hemolytic anemia, leukemia, Hodgkin's disease, malaria and syphilis. After that he made investigation on splenic anemia and described it as Splenomegalie mit Leberzirrhose in 1894[4], and in 1910[5][6][7] he postulated a nomenclature of Banti's disease, emphasizing the characteristics of this disease and specific findings of the spleen. As the cause of this disease, he presumed production of toxin in the spleen caused by unknown infection, and pointed out that pathologic feature of this disease is Fibroadenie in the spleen caused by proliferation of connective tissue.

Following the assertion of BANTI, many studies were carried out from various aspects on the disease picture of so-called Banti's disease, and discussions were heatedly made. OSLER, in 1900[36], reported cases showing the similar course as the description of BANTI, and he insisted that this might justifiably be called splenic anemia. On the other hand, however, having many autopsy cases of extrahepatic obstruction of the portal vein, german researchers as FRERICHS, in 1853[13], and SPIEGELBERG, in 1895[46], reported the cases having anemia and splenomegaly with obstructive moment in the portal vein or splenic vein. ROMMELAERE, in 1903[39], CAUCHOIS, in 1908[9], and WARTHIN, in 1910[54], described cases of extrahepatic portal occlusion. Studying histological findings of the spleen in Banti's own original case, ASCHOFF asserted that Fibroadenie, an indispensable finding of socalled Banti's disease is nothing but the finding of congestive splenomegaly. EPPINGER[12] also asserted that the finding of Fibroadenie coincides with that of congestive splenomegaly caused by extrahepatic obstruction of the portal vein. In 1927, HUECK[15] maintained that Fibroadenie of the splenic follicles observed in case of BANTI cannot be accepted to be specific to this lesion. DÜRR, in 1924[11], also studied microscopic specimen of the spleen of Banti's original case and insisted that it cannot be distinguished from those findings observed in the spleen of cases of extrahepatic obstruction of the portal vein, cirrhosis of the liver and the like. KLEMPERER, in 1936[20], studied clinical course and influence of splenectomy on the disease and he pointed out that the finding of Fibroadenie can be observed in splenomegaly of various origins. Thus, the independency of this disease as a disease unit became gradually to be denied.

On the other hand, MCINDOE[24] postulated the term of portal hypertension considering that the disturbance of blood flow in the portal vein might be the cause of congestive

splenomegaly, being based on his experiment of perfusion in cirrhotic liver. The concept of portal hypertension was employed by McMICHAEL[25] thereafter in his experiment on dogs and it was gradually established by following studies discussing the significance of portal pressure in the occurrence of splenomegaly by WHIPPLE in 1936 and determination of portal pressure in clinical cases and demonstration of elevated portal pressure by THOMPSON, COUGHY, WHIPPLE and ROUSSELOT[51]. In 1945, WHIPPLE[56] asserted classification of portal hypertension from the stand point of portal flow blook, and in this classification Banti's disease was made to belong to extrahepatic obstruction of the portal vein, and he considered that splenomegaly in this disease is congestive one caused by secondary congestion. Furthermore, in 1954, DI GUGLIELMO[10] insisted that there exists Banti's disease obviously distinguished from congestive splenomegaly from clinical and pathological aspect, though he admitted the existence of congestive splenomegaly secondary to extrahepatic portal flow block. SANTY and MARION[43] asserted also that extrahepatic portal flow block should be separately considered from resembling other lesions from their observation on 378 clinical cases, admitting the independency of Banti's disease. From the stand point of emphasizing the finding of Fibroadenie of the follicle or the splenic pulp, CASSANO, in 1958[8], insisted the dual origin of this disease as *splenomegalia fibroadenica di* BANTI and *splenomegalie fibrozo congestizie*. In our country, MITAMURA, in 1916[26], reported that histological feature of the spleen in Banti's disease obviously differes from that of Laennec's cirrhosis and he postulated the concept of Pseudoleberzirrhose. ONO[35] pointed out the pathologic changes of the artery in the spleen in Banti's disease and, particularly, the finding of hyperemia in the central artery. There are also researchers who consider this disease from stand point of splenic toxicosis as TOMODA[50] and from that of allergic etiology[48].

As has been reviewed, there are many problems left to be solved in the independency of Banti's disease, and some researchers insist that the term of Banti's disease will shortly fade away[2][19].

From the concept of congestive splenomegaly, many attempts have been done in vain to produce experimental portal hypertension or splenomegaly by obstruction or constriction of the extrahepatic portal vein. It is assumed that powerful support would be obtained for the existence of Banti's disease as a disease unit by production of disease unit resembling Banti's disease through selective impairment of the splenic tissue, even if the original definition of BANTI might be more or less modified. Here, in the present experiment, it was attempted to produce splenitis based on antigen-antibody reaction in dogs, by intravenous injection of anti-spleen serum obtained by immunizing rabbits with dog spleen homogenate[23][47].

It is known that antibody production is strongly enhanced in animals when transfer of antigen is repeated. However, this effect of enhancement works at most with the injection of about 9 times, and more injection is assumed to be meaningless. It is also admitted in general that production of antibody reaches its maximum about 1 week after the final injection of antigen[31]. In the present experiment also, immune serum was withdrawn 7 days after the final injection of immunization for 9 times.

Although the splenic tissue was exclusively used for the antigen, obtained anti-spleen serum showed cross reaction against antigen of liver in precipitation test, and the closeness

of antigenicity between the spleen and liver could not be denied, or this might be due to the antigenicity of the small vessels necessarily contained in the spleen homogenate as the antigen, although this problem could not be clarified in the present experiment.

According to SUZUKI[48)49)], splenomegaly appeared more than 30 days after protracted sensitization of rabbits with egg white albumin, and portal pressure gradually increased in parallel with the advancement of the sensitization. Elevation of portal pressure was reversible and it showed the tendency of decrease when the sensitization of more than 30 days was interrupted[34)]. In the present experiment, portal pressure increased as early as 5 days after the initial injection of anti-spleen serum, which further increased on with the repeat of the injection. Concerning the mechanism of elevation of portal pressure observed in the present experiment, it was presumed that the elevation of portal pressure was due to some functional changes at least during the period of the observation in the present experiment, judging from the facts that elevated portal pressure restore to the previous level by interruption of the injection for more than 30 days, and that hepatic changes adequately explainable of portal hypertension could not be demonstrated histologically even when portal pressure actually elevated.

Concerning elevation of portal pressure and histological changes in the liver, THOMPSON[51)] and PATEK[37)] respectively asserted that there is no correlation between these two, the former from clinical observations and the latter from observations of portal hypertension and liver findings in his experiment of intravenous injection of human serum albumin. In our country, KIMOTO[17)18)] also could not find out any correlation between the intensity of portal hypertension and that of cirrhotic change of the liver from clinical observations. YAMADA[58)59)] pointed out that there exist some occasions of portal hypertension even in cases without significant changes of the liver of rabbits sensitized with egg white albumin. In the present experiment also, any definite correlation could not be observed between portal hypertension and hepatic change, and also between the former and splenic change. In the animals experimentally well aged, elevation of portal pressure naturally lasted for long and in these cases such changes as cellular infiltration could be observed around the vessels in the liver, which should be interpreted to be the secondary change due to long lasted elevation of portal pressure[28)]. Although only a single case in the present experiment, a picture of early stage of hepatic fibrosis could be observed. If such hepatic fibrosis develops further, it is assumed that hepatic vascular resistance will increase with resulting irreversible elevation of portal pressure as was pointed out by HERRICK and MCINDOE. In such a stadium, other findings of edema, devastation, cellular infiltration, thickening, constriction and decrease in number would be naturally observed in the intrahedatic fine tributaries of the portal venous system besides therabove mentioned fibrosis[42)].

Splenomegaly could not be observed at least within the period of observation in the present experiment. However, a picture of acute splenitis was observed revealing the findings such as increase in wandering cells of various kind, eventual infiltration of polymorphnuclear leucocytes in the red pulp[1)27)] and atrophy or disappearance of the follicles, which was taken place by increase in plasma cells and reticulum cells terminating finally in increase in fibrous element. A series of these findings developing in determinative direction was identical to those of animals of protracted sensitization which terminates in atrophic picture

of tissue exhaustion as was observed by HOJO[32)33)].

It is difficult to assume, considering from the essential character existing in the present experiment, that the observed splenic changes are secondary to long lasted portal hypertension and absolutely attributable to the congestion accompanying to elevation of portal pressure, as is obviously understood from the results of experiment of splenic venous ligation in sensitized rabbits with egg white albumin by SUZUKI[45)48)].

The spleen of control animals showed histologically only an increase in wandering cells at most, revealing an obviously different attitude from those in experimental animals. This fact proposes the existence of specific effect of anti-spleen serum essentially different from the effect of normal rabbit serum. When considered together with the finding that portal pressure did not elevate in control animals, peculiarity of the splenic changes in the present experiment is accepted to provide some suggestion to the independency of Banti's disease.

In addition, changes of the peripheral blood, particularly marked decrease in thrombocytes seemed to correspond to the reaction in the spleen. According to KARIYONE[16)], degree of change in white blood cell count has correlation with that of splenomegaly to some extent. However, in the present experiment, splenomegaly could not be observed at least within the period of the observation as mentioned in the above, and white blood cell count did not reveal uniform change partly owing to the influence of laparotomy frequently performed.

It is widely admitted at present that the findings of *Fibroadenie* and *Sinushyperplasie* as a specific histological change of Banti's disease respectively reported by BANTI[6)] and DÜRR[11)] are not specific exclusively to Banti's disease. In the present experiment, portal hypertension could be observed in all cases from an early period of the injection of anti-spleen serum, and in the spleen a picture of acute splenitis with increase in wandering cells could be observed initially, which was followed by increase in plasma cells and reticulum cells finally terminating in atrophic or fibrotic changes. In some cases, narrowing of the splenic sinus was observed. In the liver, fibrosis could be observed around the vessels in some cases, although in the initial stage significant histological change could not be found. Among cell components in peripheral blood, remarkable decrease in thrombocytes was ascertained. It is assumed that these findings obtained are identical to those of Banti' disease in the early stage. It is assumed that these changes in the spleen and liver may possibly advance to Fibroadenie in the spleen and fibrosis in the liver, judging from the fact that the finding of generally accepted Fibroadenie is the terminal picture of splenitis[44)] and Fibroadenie can appear regardless of the kind of the cause[20)].

There can be seen many report on the role of the liver in Banti's disease. From the clinical observations of Banti's disease, ITO[21)29)] and others presumed that in this lesion some common factors act simultaneously on the spleen and liver. From studies on splenomegaly in autopsy cases, KURIBAYASHI[22)] considered that etiologic factor effecting on the liver is essential and the splenic changes are secondary ones due to the hepatic change. WATANUKI[53)] asserted, from his autopsy studies of splenomegaly, that the splenic changes in Banti's disease are those of splenitis induced by concomitantly existing hepatitis, which is modified by portal hypertension accompanying to changes in the intrahepatic fine tribu-

taries of the portal vein, and there acts some allergic mechanism. Even though it is too conservative to assume that etiologic factor of the splenic change in this disease cannot be sought merely in portal hypertension[38], it was demonstrated in the present experiment that essential changes in Banti's disease can exist in the spleen and development of portal hypertension was presumed to be due to the mechanism displayed functionally within the liver[30]. The author is convinced from the results of the present experiment that Banti's disease develops having its origin in the spleen or spleen and liver.

V. SUMMARY

1) By the repeated intravenous injection of anti-spleen serum, portal hypertension was able to be produced in dogs. This portal hypertension, being reversible and deprived of corresponding hepatic changes, it was presumed to be based on some functional changes.

2) In parallel with elevation of portal pressure, red blood cell count and hemoglobin content showed the tendency of decrease, particularly decrease in thrombocytes being remarkable.

3) In the spleen in animals with long lasted portal hypertension, picture of splenitis or increase in wandering cells could be observed initially, which was taken place by increase in plasma cells and reticulum cells terminating in atrophic or fibrotic changes.

4) Histological changes of the liver did not necessarily develop in parallel with that of the spleen, and in some cases of long time observation an increase in fibrous element was observed, suggesting the possibility of advancement to fibrosis.

5) From these findings, it is assumed that Banti's disease develops having its origin in the spleen or spleen and liver.

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(* in Japanese)

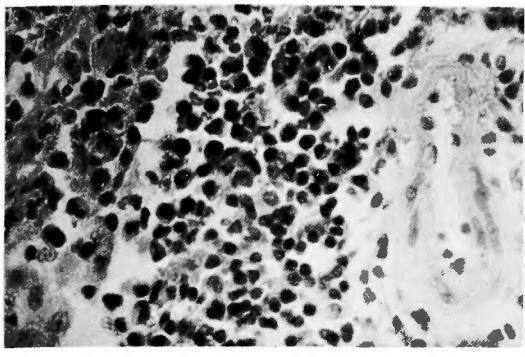

Fig. 9 Picture of splenitis and increase in wandering cell of various kinds. H-E ×400

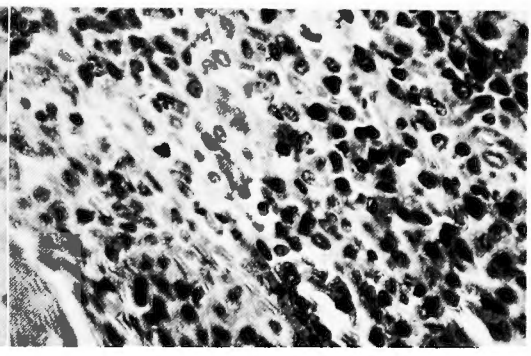

Fig. 10 Marked increase in plasma cells and reticulum cells, and narrowing of the splenic sinuses. H-E ×400

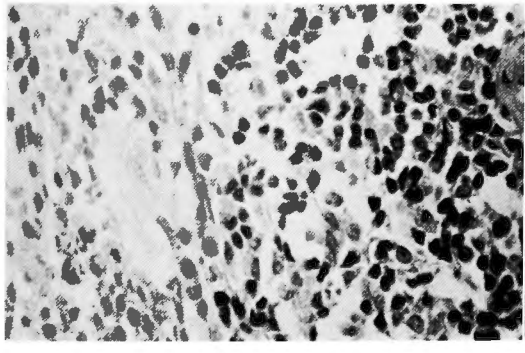

Fig. 11 Outstanding increase in fibrous element in the spleen, being accompanied by infiltration of plasma cells and reticulum cells. H-E ×400

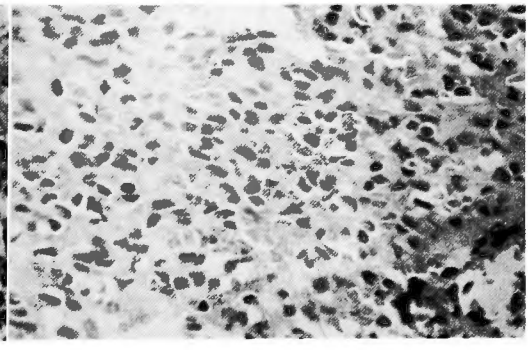

Fig. 12 Atrophic finding of the spleen. H-E ×400

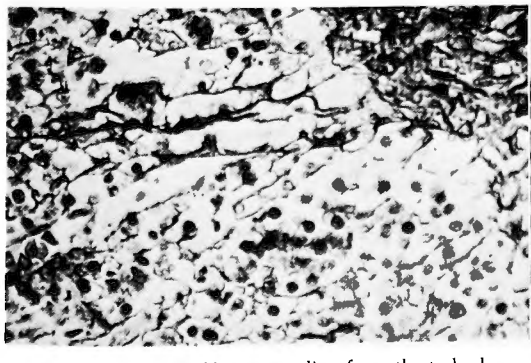

Fig. 13 Lattice fibres extending from the trabecle in the spleen. Gomori ×400

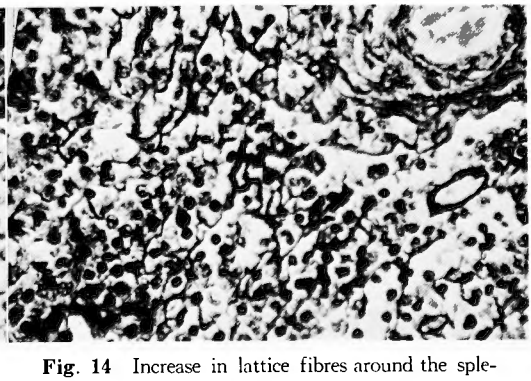

Fig. 14 Increase in lattice fibres around the splenic follicles. Gomori ×400

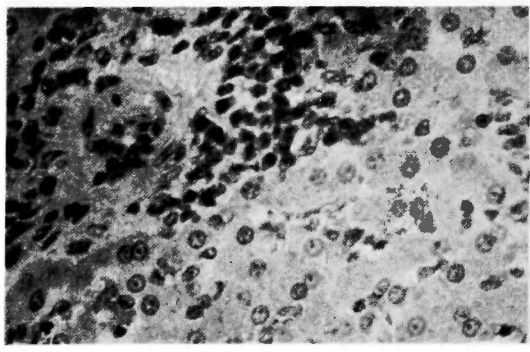

Fig. 15 Cellular infiltration in Glisson's sheath. H-E ×400

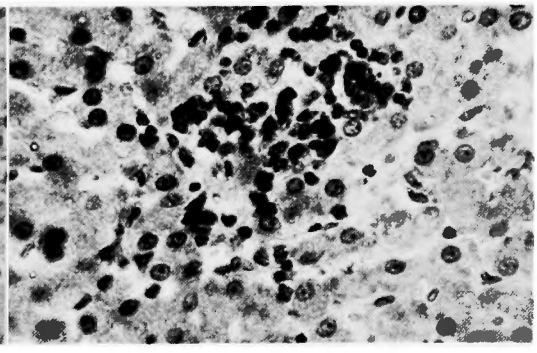

Fig. 16 Infiltration of wandering cells around the hepatic central vein. H-E ×400

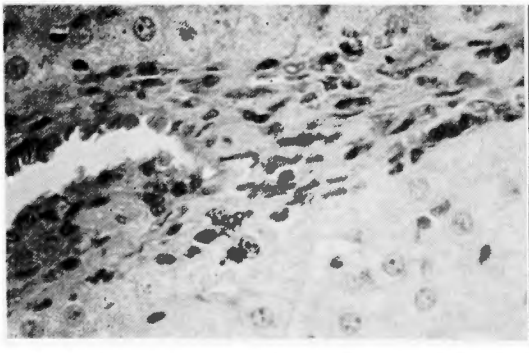

Fig. 17 Plasma cells and fibroblasts in Glisson's sheath. H-E ×400

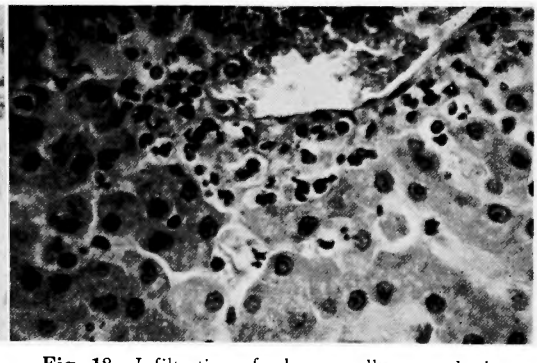

Fig. 18 Infiltration of plasma cells around the hepatic central vein. H-E ×400

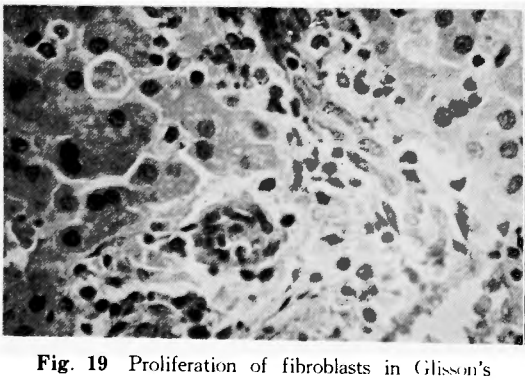

Fig. 19 Proliferation of fibroblasts in Glisson's sheath. H-E ×400

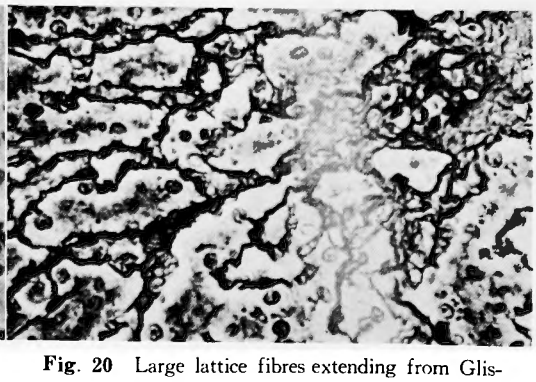

Fig. 20 Large lattice fibres extending from Glisson's sheath. Gomori ×400

和文抄録

実験的門脈圧亢進症における肝および脾の態度

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著者は犬脾ホモジネートを抗原として家兎を感作して得た抗犬脾家兎血清を，犬に週1回反覆静注することによつて，全例に門脈圧の上昇を認めた．この上昇は可逆性であり，同時に肝には変化が乏しいことから機能的上昇と考えざるを得ない．

門脈圧の上昇とともに，末梢血中の赤血球・血色素は減少傾向を示し，血小板は著明に減少する．

門脈圧上昇持続犬の脾は，初期に脾炎像ともいうべき各種遊走細胞の増加，ついで形質・細網細胞反応に代り，遂に萎縮像ないし線維増生性変化を呈する．

肝の組織学的変化は，脾の変化程度と必ずしも並行しないが，長期観察例では線維成分の増加をみるものもあり，Fibrose への進展を推測せしめる．

以上より所謂 Banti 病は脾原発性にあるいは肝脾原発性に成立し得るもので，独立疾患としての意義を有するものと考える．